Molecular Interactions in Pharmaceutical Compounds

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MS10-O2 Molecular Interactions in Pharmaceutical Compounds

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Small organic molecules, especially in the pharmaceutical sciences, tend to crystallise in a plethora of different crystal forms, either as pure compounds or with the inclusion of solvent molecules. Due to their changed physico-chemical characteristics, such as melting point, compressibility, solubility and thus bioavailability, and physical and chemical stability, different crystal forms can pose a problem to the manufacture of medicines.[1] It is thus crucial to understand the crystallisation behaviour and manufacturability of these compounds in order to avoid problems in the life-time of the medicine and costly recalls comparable to ritonavir[2] or rotigotine.[3] Bioactive molecules and pharmaceuticals typically have multiple functional groups, enabling them to interact with receptors and thus show pharmacological action. In the solid-state, the interactions through these functional groups are the driving forces of molecular recognition. By applying X-ray and neutron diffraction methods as well as thermoanalysis, vapour sorption and spectroscopic analysis in combination with computational techniques, we are probing the strong and weak interactions within the crystal forms and during the crystallisation in order to understand and predict their characteristics.

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Keywords: Polymorphism, Pharmaceutical, Molecular recognition

MS10-O3 High resolution neutron and X-ray diffraction RT studies of an H-FABP – Oleic acid complex: study of the internal water cluster and the ligand binding by a transferred multipolar electron density distribution

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Crystal diffraction data of heart fatty acid binding protein (H-FABP) in complex with oleic acid were measured at room temperature with high resolution X-ray and neutron protein crystallography (0.98 Å and 1.90 Å resolution respectively). These data provided very detailed information about the cluster of water molecules and the bound oleic acid in the H-FABP large internal cavity. The jointly refined X-ray/neutron structure of H-FABP was complemented by a transferred multipolar electron density distribution using the parameters of the ELMAM2 library. The resulting electron density allowed a precise determination of the electrostatic potential in the fatty acid (FA) binding pocket. Bader's quantum theory of atoms in molecules was then used to study interactions involving the internal water molecules, the FA and the protein. This approach showed H-H contacts of the FA with highly conserved hydrophobic residues known to play a role in the stabilization of long chain FAs in the binding cavity. The determination of water hydrogen (deuterium) positions allowed the analysis of the orientation and electrostatic properties of the water molecules in the very ordered cluster. As a result, a significant alignment of the water molecules permanent dipoles with the protein electrostatic field was observed. This can be related to the dielectric properties of hydration layers around proteins, where the shielding of electrostatic interactions depends directly on the rotational degrees of freedom of the water molecules in the interface.

Keywords: Neutron protein crystallography ; High resolution room temperature X-ray crystallography; Fatty acid binding protein; Protein hydration layer ; AIM Topological properties